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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/756,948	01/13/2004	Martin W. Brechbiel	4239-67017-01	3278

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KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET
SUITE #1600
PORTLAND, OR 97204-2988

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/756,948	BRECHBIEL ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/21/04,1/18/05,10/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-10,12,13,15,17-19,21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10).

3. Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10) teaches of the method for lymphatic system imaging via intracutaneous administration of a G8 dendrimer conjugate to mouse and imaging lymphoproliferative/lymphoma with 0.1 mmol Gd/kg. The use of Gd-1B4M-PAMAM-G8 allows for visualizing the deep lymphatic system, such as the lymph nodes and lymphatic vessels as seen in figure 6 where the arrows indicate lymph node swelling (p6, last paragraph; p7). In addition, this method was able to distinguish the appearance of infection expansion of lymphocytes from either chronic lymphoproliferative or neoplastic conditions (see p7 and p8, paragraph 1). The 1B4M-DTPA metal chelates are described for use with all PAMAM dendrimers of generations 2-10 (p2, column 2, last paragraph).

4. Claims 1,2,4-9,12,13,15-19,21 and 22 are rejected under 35 U.S.C. 102(a) as being anticipated by Kobayashi et al. (*Magn. Reson. Med.* **2003**, *50*, 758-765).

5. Kobayashi et al. (*Magn. Reson. Med.* **2003**, *50*, 758-765) teaches of the method of lymphatic system imaging via MRL (magnetic resonance lymphangiography (p758, paragraph 1). The method involves intravenous administration of 0.005 mmol Gd/kg of PAMAM-G8-1B4M-Gd into mice to visualize the lymph vessels (fig 2; p758, last paragraph). Other PAMAM dendrimer conjugates were prepared, such as PAMAM-G4 and G5, DAB-G5, etc. and used according to the method (p759, paragraph 1; table 1; p760, Dynamic 3D-micro-MRL). The contrast agents above allowed for deep lymph node visualization (p761, results), showed systemic dilation of the lymphatic vessels for the mice presenting lymphangitis and showed considerable lymph node swelling with the central filling defects (non-enhanced area) for the lymphoproliferative/lymphoma mice models (p762, paragraphs 2 and 3). The indication of metastatic tumor cells was confirmed by 3D-MRL with PAMAM-G8 as the image obtained did not show any abnormalities in either the lymph node or lymph vessels and that the tumor cells in the lymph node specifically caused the abnormal image obtained (p763, paragraphs 1 and 3).

6. Claims 1,2,4-9,12,13,15,18,19,21 and 22 are rejected under 35 U.S.C. 102(a) as being anticipated by Kobayashi et al. (*Cancer Research* **2003**, *63*, 271-276).

7. Kobayashi et al. (*Cancer Research* **2003**, *63*, 271-276) teaches of a method of MRI lymphatic system imaging with the contrast agent, Gd(III)1B4M-PAMAM-G8 (p272, paragraphs 1 and 3; p273, paragraph 1). The administration of 0.005 mmol Gd/kg contrast agent was via intracutaneous injection for lymph node and lymphatic vessel

visualization (p273, paragraph 3; fig 2). Dilation of the lymphatic vessels was observed in mice having lymphangitis (infection), proliferative or neoplastic lymph node swelling (with non-enhancing central filling defects) in a lymphoproliferative model and inflammatory lymph node swelling in an infection/inflammation model (p274, paragraph 2; abstract; p275, paragraph 1).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-10,12-25,27-29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) in view of Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10) and further in view of Baker, Jr. et al. (US 6,471,968B1).

10. Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) discloses the method of identifying a lymph node into which lymph fluid flows from a tumor for breast sentinel lymph node (first lymph node) mapping (p35, paragraph 1; p36, paragraph 2). The method involves imaging the lymph node and lymphatic vessel draining from the injection site using MR lymphography and the contrast agents used are gadopentetate dimeglumine, Gd-DTPA-PE-POE and SPIO particles (p36, paragraph 2; p37, results; p41, paragraph 7). MR lymphography is advantageous for visualizing focal lymph

draining from a breast tumor since the results show that MR lymphography provided for visualization only of the lymphatic drainage from the injection site of the contrast agents. Upon peritumoral or periareolar injection of the contrast agent, visualization of lymphatic drainage from early state breast tumors was accomplished (p41, paragraphs 4 and 5). Also disclosed is that surgical biopsy of the sentinel lymph node is a standard practice for minimally invasive surgery in early stages of breast cancer (p35, paragraph 1). Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) does not disclose the use of PAMAM contrast agents for the method of identifying a lymph node into which lymph fluid flows from a tumor.

11. Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10) teaches the method for lymphatic system imaging via administration of a G8 dendrimer conjugate to mouse and imaging lymphoproliferative/lymphoma with 0.1 mmol Gd/kg as well as that stated above. Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10) also discloses that USPIO particles have been utilized in the past to image the lymphatic system (p6, lymphatic MRI contrast agents). The USPIO particles negatively enhance normal lymph nodes, thus providing for a much smaller signal which makes the lymph node difficult to find and it cannot detect the lymphatic vessels.

12. At the time of the invention it would have been obvious to one ordinarily skilled in the art to use any of the generations 2-10 and the 1B4M-DTPA metal chelate for all PAMAM dendrimers (Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10); p2, column 2, last paragraph) for the methods of identifying a lymph node into which lymph fluid flows from a tumor and method for lymphatic system imaging. The PAMAM dendrimer contrast

agents allow for enhanced resolution and small doses of the agents allows for visualization of the entire deep lymphatic system. Substitution of the PAMAM dendrimers for the gadopentetate dimeglumine, Gd-DTPA-PE-POE, SPIO particles of Suga et al. would be obvious as Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10) clearly states that they allow for clear visualization of the entire lymphatic system, including the deep lymphatic system while the SPIO agents lack the ability to image the entire lymphatic system, such as lymphatic vessels. One skilled in the art would have a great expectation of success for using the PAMAM dendrimers to accurately detect and visualize infection and tumors of the entire lymphatic system, including the deep lymphatic system.

13. Also it would have been obvious to one skilled in the art to inject the PAMAM dendrimer contrast agent into a tumor site (intratumorally) to visualize the lymphatic vessel draining from the tumor site as Suga et al. discloses that MR lymphography provides for visualization from the site of injection of the contrast agent or peritumorally as is described above. The importance of surgical biopsy of the sentinel lymph node is described for early stages of breast cancer and it is advantageous to use this procedure concurrently with the technique of imaging the lymphatic system with the PAMAM dendrimer contrast agents as they allow for a more reliable method of detecting tumors in the lymphatic system. This will guarantee that the correct site is being biopsied.

14. Baker, Jr. et al. (US 6,471,968B1) discloses the use of a fluorescent tagged (column 7, lines 7) Gd-PAMAM dendrimer conjugate (column 3, line 13; column 6, line 63) for visualizing the location of diseased cells, such as a tumor and monitoring the

response to therapy via MR imaging (column 2, lines 30-40; column 10, lines 65+ to column 11, lines 1-5). The fluorogenic marker not only allows for the locating of a tumor but also allows for the visualization of response to treatment with therapeutic agents.

15. The Gd-1B4M-PAMAM-G8 dendrimer of Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10) are tailored to target the lymphatic system and distinguish the diseased portion, such as a tumor of the lymph nodes. It would be obvious to one skilled in the art to use a fluorescent tag for the Gd-1B4M-PAMAM-G8 dendrimer of Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10) to monitor the response to the treatment of tumors found in the lymphatic system to assure that the cancer has been fully eradicated.

16. Claims 1,2,4-9,12-29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) in view of Kobayashi et al. (*Magn. Reson. Med.* **2003**, *50*, 758-765) and further in view of Baker, Jr. et al. (US 6,471,968B1).

17. Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) discloses the method of identifying a lymph node into which lymph fluid flows for breast sentinel lymph node (first lymph node) mapping (p35, paragraph 1; p36, paragraph 2). The contrast agents used for MR lymphography are gadopentetate dimeglumine, Gd-DTPA-PE-POE, SPIO particles and the method involves imaging the LN and lymphatic vessel draining from the injection site as well as that stated above. Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) does not disclose the use of PAMAM contrast agents for the method of identifying a lymph node into which lymph fluid flows from a tumor.

18. Kobayashi et al. (*Magn. Reson. Med.* **2003**, *50*, 758-765) teaches of the method of lymphatic system imaging via MRL (magnetic resonance lymphangiography (p758, paragraph 1). The method involves intravenous administration of 0.005 mmol Gd/kg of PAMAM-G8-1B4M-Gd into mice to visualize the lymph vessels as well as that stated above. Kobayashi et al. (*Magn. Reson. Med.* **2003**, *50*, 758-765) also discloses that the Gd-DTPA-dimeglumine was examined for the method of lymphatic system imaging via MRL but did not allow for most of the lymph nodes to be visualized (p761, results) and that in comparison PAMAM-G8 allowed for better visualization of the lymphatic vessels (p762, column 2, paragraph 1).

19. At the time of the invention it would have been obvious to one ordinarily skilled in the art to utilize the PAMAM dendrimer contrast agents of Kobayashi et al. (*Magn. Reson. Med.* **2003**, *50*, 758-765) as an alternative to the gadopentetate dimeglumine, Gd-DTPA-PE-POE, SPIO particles of Suga et al. The PAMAM dendrimer contrast agents allow for enhanced resolution and small doses of the agents allows for visualization of the entire deep lymphatic system. The Gd(III)1B4M-PAMAM-G8 has a large size and low transvascular diffusion which allows for it to be retained in fine lymphatic vessels as well as the lymph nodes for an extended period of time, resulting in a high signal:background ratio. Substitution of the PAMAM dendrimers for the gadopentetate dimeglumine, Gd-DTPA-PE-POE, SPIO particles of Suga et al. would be obvious as Kobayashi et al. (*Magn. Reson. Med.* **2003**, *50*, 758-765) clearly states that they are allow for clear visualization of the entire lymphatic system, including the deep lymphatic system while the SPIO agents lack the ability to image the entire lymphatic

system, such as lymphatic vessels. One skilled in the art would have a great expectation of success for using the PAMAM dendrimers to accurately detect and visualize infection and tumors of the of the entire lymphatic system, including the deep lymphatic system.

20. Also it would have been obvious to one skilled in the art to inject the PAMAM dendrimer contrast agent into a tumor site (intratumorally) to visualize the lymphatic vessel draining from the tumor site as Suga et al. discloses that MR lymphography provides for visualization from the site of injection of the contrast agent or peritumorally as is described above. The importance of surgical biopsy of the sentinel lymph node is described for early stages of breast cancer and it would be obvious to use this procedure concurrently with the technique of imaging the lymphatic system with the PAMAM dendrimer contrast agents as they allow for a more reliable method of detecting tumors in the lymphatic system. This will guarantee that the correct site is being biopsied.

21. Baker, Jr. et al. (US 6,471,968B1) discloses the use of a fluorescent tagged (column 7, lines 7) Gd-PAMAM dendrimer conjugate (column 3, line 13; column 6, line 63) for visualizing the location of diseased cells, such as a tumor and monitoring the response to therapy via MR imaging as well as that stated above.

22. The Gd-1B4M-PAMAM-G8 dendrimer of Kobayashi et al. (*Mol. Imaging* **2003**, 2, 1-10) are tailored to target the lymphatic system and distinguish the diseased portion, such as a tumor of the lymph nodes. It would be obvious to one skilled in the art to use a fluorescent tag for the Gd-1B4M-PAMAM-G8 dendrimer of Kobayashi et al. (*Mol.*

Imaging **2003**, *2*, 1-10) to monitor the response to the treatment of tumors found in the lymphatic system to assure that the cancer has been fully eradicated.

23. Claims 1,2,4-9,12-16,18-26,29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) in view of Kobayashi et al. (*Cancer Research* **2003**, *63*, 271-276) and further in view of Baker, Jr. et al. (US 6,471,968B1).

24. Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) discloses the method of identifying a lymph node into which lymph fluid flows for breast sentinel lymph node (first lymph node) mapping (p35, paragraph 1; p36, paragraph 2). The contrast agents used for MR lymphography are gadopentetate dimeglumine, Gd-DTPA-PE-POE, SPIO particles and the method involves imaging the LN and lymphatic vessel draining from the injection site as well as that stated above. Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) does not disclose the use of PAMAM contrast agents for the method of identifying a lymph node into which lymph fluid flows from a tumor.

25. Kobayashi et al. (*Cancer Research* **2003**, *63*, 271-276) teaches of a the method of MRI lymphatic system imaging with the contrast agent, Gd(III)1B4M-PAMAM-G8 as well as that stated above. Kobayashi et al. (*Cancer Research* **2003**, *63*, 271-276) also discloses that deep lymph nodes were not visualized with Gd-DTPA-dimeglumine and that the lymphatic vessels were better visualized with PAMAM-G8 than with Gd-DTPA-dimeglumine (p274, results).

26. At the time of the invention it would have been obvious to one of ordinary skill in the art to inject the PAMAM dendrimer contrast agent into a tumor site (intratumorally) to visualize the lymphatic vessel draining from the tumor site as Suga et al. discloses that MR lymphography provides for visualization from the site of injection of the contrast agent or peritumorally as is described above. The importance of surgical biopsy of the sentinel lymph node is described for early stages of breast cancer and it would be obvious to use this procedure concurrently with the technique of imaging the lymphatic system with the PAMAM dendrimer contrast agents as they allow for a more reliable method of detecting tumors in the lymphatic system. This will guarantee that the correct site is being biopsied.

27. One of ordinary skill in the art would be motivated to substitute the gadopentetate dimeglumine of Suga et al. for the Gd(III)1B4M-PAMAM-G8 of Kobayashi et al. (*Cancer Research* **2003**, *63*, 271-276). The Gd(III)1B4M-PAMAM-G8 has a large size and low transvascular diffusion which allows for it to be retained in fine lymphatic vessels as well as the lymph nodes for an extended period of time, resulting in a high signal:background ratio (p275, paragraph 4). Also, in comparison to SPIO particles, the Gd(III)1B4M-PAMAM-G8 contrast agent is able to visualize subtle changes in small lymph nodes and lymphatic vessels because it is a positive contrast agent as opposed to the SPIO particles, a negative contrast agent. The SPIO particles provide for a much smaller signal which make the lymph node difficult to find and it cannot detect the lymphatic vessels (Kobayashi et al. (*Cancer Research* **2003**, *63*, 271-276; p275, paragraph 5). One skilled in the art would have a great expectation of success for using

the PAMAM dendrimers to accurately detect and visualize infection and tumors of the of the entire lymphatic system, including the deep lymphatic system.

28. Baker, Jr. et al. (US 6,471,968B1) discloses the use of a fluorescent tagged (column 7, lines 7) Gd-PAMAM dendrimer conjugate (column 3, line 13; column 6, line 63) for visualizing the location of diseased cells, such as a tumor and monitoring the response to therapy via MR imaging as well as that stated above.

29. The Gd-1B4M-PAMAM-G8 dendrimer of Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10) are tailored to target the lymphatic system and distinguish the diseased portion, such as a tumor of the lymph nodes. It would be obvious to one skilled in the art to use a fluorescent tag for the Gd-1B4M-PAMAM-G8 dendrimer of Kobayashi et al. (*Mol. Imaging* **2003**, *2*, 1-10) to monitor the response to the treatment of tumors found in the lymphatic system to assure that the cancer has been fully eradicated.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
March 23, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER